## REMARKS

Claims 1, 3-5, 14, 21 and 22 are pending after entry of the amendments set forth herein.

Claims 1 and 22 are amended. Support for these amendments is found throughout the specification, at, for example, page 8, lines 2-3 and page 40, lines 1-4.

No new matter is added.

### OBJECTIONS TO THE CLAIMS

Claims 3-5, 14 and 21-22 are objected to for depending from an indefinite claim.

Claim 1 has been amended to address the 35 U.S.C. 112, second paragraph rejection. Accordingly, this objection may be withdrawn.

### REJECTIONS UNDER §112, ¶2

Claims 1, 3-5, 14, 21 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants have amended the claims to recite "loss of neurogenesis resulting from neuroinflammation" rather than "loss of neurogenesis capacity resulting from neuroinflammation." Reconsideration and withdrawal of the rejection is requested.

### REJECTIONS UNDER §103(A)

I. Claims 1, 3, 14 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Brain Res 791: 352-356, 1998), in view of Plevova, (Radiol Oncol 36: 33-40, 2002), as evidenced by Monje et al. (Nat Med 8: 955-962, 2002), and Kyrkanides et al. (Mol Brain Res. 104: 159-169, 2002).

Claim 1, upon which Claims 3, 14 and 21-22 depend, is drawn to a method of reducing loss of neurogenesis resulting from neuroinflammation due to cranial irradiation in an individual, and recites "contacting said individual with a dose of a non-steroidal anti-inflammatory drug (NSAID) that crosses the blood-brain barrier . . . wherein said loss of neurogenesis resulting from neuroinflammation due to said cranial irradiation in an individual is reduced".

Applicants submit that the cited combination of art does not make obvious the pending claims. The primary reference, Kondo et al., teaches that ischemia induces delayed hippocampal neuronal cell death, and that indomethacin treatment significantly protects against this death (abstract, Fig. 1, Fig. 2). However, relevant to the presently claimed invention, Kondo et al. do not teach that neuroinflammation is induced in their studies, nor that the cell death that they have observed following ischemia affects neurogenesis. Kondo teaches death of mature neurons, whereas neurogenesis is the production and differentiation of new neurons.

Furthermore, Applicants assert that it is well-known and well-documented that ischemia, although damaging to differentiated neurons, is associated with an increase in neurogenesis, not a decrease; see, for example, the teachings of Liu et al ((1998) J Neurosci. 18(19):7768-78) (Exhibit A) and Yamashima T, et al. ((2007) Biotechnol J. 2(5):596-607) (Exhibit B).

Because Kondo et al. do not teach neuroinflammation or neurogenesis, because neuroinflammation is not inherently associated with ischemia, and because ischemia-induced cell death is not inherently associated with loss of neurogenesis, Kondo et al. cannot teach the presently claimed methods, which relate to methods for reducing loss of neurogenesis resulting from neuroinflammation due to cranial irradiation in an individual.

In making this rejection, the Examiner asserts the following on page 6, lines 1-5:

> 15. Kondo et al. teach the effect of indomethacin in gerbils induced with cerebral ischemia leading to neuroinflammation. Indomethacin resulted in delayed hippocampal neuronal cell death and reduced apoptosis detected by TUNEL assay (abstract; Figures 2, 3), thereby reducing loss of neurogenesis capacity. The reference also teaches that indomethacin crosses the BBB (page 352, col 1, para 2).

Applicants submit that in making the rejection, the Examiner has extrapolated beyond what the reference teaches to reach these conclusions, indeed ignoring common knowledge in the art that ischemia stimulates neurogenesis.

The Examiner asserts in the first sentence of the above passage that "Kondo et al. teach the effect of indomethacin in gerbils induced with cerebral ischemia leading to neuroinflammation" (emphasis included). However, Kondo et al. are actually silent on the topic of neuroinflammation, and thus it is improper to assert that neuroinflammation contributed to the

ischemia-induced cell death observed by Kondo et al. Likewise, the Examiner extrapolates that Kondo et al., by teaching hippocampal neuronal cell death and apoptosis, are teaching loss of neurogenesis. However, Kondo et al. do not actually teach loss of neurogenesis, much less loss of neurogenesis induced by ischemia. Indeed, Kondo et al. are silent on neurogenesis.

In view of the knowledge in the art and the absence of teachings by Kondo et al. on neurogenesis, it is improper to extrapolate or conjecture that neurogenesis was inhibited by the ischemia induced in Kondo et al.'s studies. In fact, the art of Liu et al. and Yang et al. teaches the opposite. Thus, Kondo does not teach or suggest that neuroinflammation results in reduced neurogenesis.

When Kondo et al. is read for what it actually teaches, one of ordinary skill in the art is not taught by Kondo et al. that ischemia correlates with neuroinflammation. One of ordinary skill in the art is not taught by Kondo et al. that neuroinflammation results in a loss of neurogenesis. Accordingly, Kondo et al. do not make obvious a method of reducing loss of neurogenesis resulting from neuroinflammation due to cranial irradiation in an individual.

The secondary reference fails to remedy the deficiencies of the primary reference. Plevova et al. were cited for teaching ionizing radiation (p. 6, l. 10-12). The Examiner asserts that Plevova et al. teach that ionizing radiation induces an immune response. Applicants note that Plevova et al. is a review article, and that the specific citation made therein with respect to brain edema and inflammation is Tada et al., which teaches that cranial irradiation produces edema and necrosis, but provides no teaching on the effect of cranial irradiation, or any neuroinflammation arising therefrom, on neurogenesis.

Plevova et al. (and by citation, Tada et al.) do not teach that neuroinflammation, or more particular, neuroinflammation arising from ionizing radiation, results in loss of neurogenesis. Plevova et al. provide no teaching on the effect of cranial irradiation, or any neuroinflammation arising therefrom, on neurogenesis. Indeed, Plevova et al. is silent on neurogenesis. Accordingly, the combination of references would not allow one to predict with any expectation of success that contacting an individual with a dose of an NSAID will reduce loss of neurogenesis resulting from neuroinflammation.

Moreover, Applicants submit that even if the asserted associations between ischemia or cranial radiation and loss of neurogenesis were inherently true, one of ordinary skill in the art would still not have found obvious the pending claimed invention.

The present claims are directed to methods of reducing loss of neurogenesis, based on the unexpected findings of the inventors that neuroinflammation causes a decrease in neurogenesis. In order to devise a method of this type, the ordinary skilled artisan would have had to know and recognize that 1) loss of neurogenesis did occur (which is false in the case of ischemia) and 2) it was the neuroinflammation that caused a loss of neurogenesis. If the ordinary skilled artisan did not know and recognize that neuroinflammation is the cause of the loss of neurogenesis, how could the ordinary skilled artisan have arrived at the pending claimed method of reducing loss of neurogenesis in an individual by contacting that individual with an agent that reduces neuroinflammation? Absent an explicit teaching of this nexus between neuroinflammation and loss of neurogenesis, the methods of the invention are not obvious to one of ordinary skill in the art.

Monje et al. was cited as evidence that cranial irradiation results in neuroinflammation, activation of microglial cells and loss of neurogenesis. (p. 6, l. 12-14)

Applicants provide herewith a Declaration under CFR 1.132 by the inventor, Dr. Theo Palmer, that states that Monje et al. is the Applicants' own work, and was published within one year of the Applicants' filing date. In view of this Declaration, Monje et al. is not citable with respect to the present invention. Additionally, Applicants submit that to their knowledge, no other references (other than those of the Applicants) exist prior to filing of the pending application that teach that neuroinflammation in general, and cranial irradiation-induced neuroinflammation in particular, results in loss of neurogenesis. Absent any other art provided by the Examiner that may provide such a teaching, Plevova et al. does not remedy the deficiencies of Kondo et al. to provide for the method recited in the pending claims.

Kyrkanides et al. was cited as evidence that one of ordinary skill in the art would be motivated "to use indomethacin in models of cranial irradiation based on evidence showing that cyclooxygenase 2 or COX-2 mRNA is induced in the mouse brain following irradiation in a dose dependent manner, as well as in ischemic cerebral injury." (p. 7, l. 3-7)

Applicants submit that Kyrkanides et al. do not teach that neuroinflammation results in loss of neurogenesis, and thus do not provide evidence that would motivate one to modify or combine any of the cited art to provide for a method of reducing loss of neurogenesis resulting from neuroinflammation due to cranial irradiation.

In view of the above arguments, reconsideration and withdrawal of the rejection is requested.

II. Claims 1, 3-5, 14 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tada et al. (Neurosurgery 41: 209-219, 1997 – online publication 1-18 pages), in view of Plevova, (Radiol Oncol 36: 33-40, 2002), as evidenced by Monje et al. (Nat Med 8: 955-962, 2002).

Claim 1, upon which Claims 3- 5 14, and 21-22 depend, is drawn to a method of reducing loss of neurogenesis resulting from neuroinflammation due to cranial irradiation in an individual, and recites "contacting said individual with a dose of a non-steroidal anti-inflammatory drug (NSAID) that crosses the blood-brain barrier . . . wherein said loss of neurogenesis resulting from neuroinflammation due to said cranial irradiation in an individual is reduced".

Applicants submit that the cited combination of art does not make obvious the pending claims. The primary reference, Tada et al., teaches that cranial irradiation produces edema and necrosis, and that dexamethasone may protect against the cranial irradiation-induced edema but not necrosis (Abstract, last paragraph). However, relevant to the presently claimed invention, Tada et al. do not teach that neuroinflammation, or more particular, neuroinflammation arising from cranial irradiation, results in loss of neurogenesis. Tada et al. provide no teaching on the effect of cranial irradiation, or any neuroinflammation arising therefrom, on neurogenesis. Indeed, Tada et al. are silent on neurogenesis. Accordingly, Tada et al. do not make obvious a method of reducing loss of neurogenesis resulting from neuroinflammation due to cranial irradiation in an individual.

The secondary reference does not remedy the deficiencies of the primary reference. Plevova et al has been cited for the reasons set forth in rejection 1. However, Applicants submit that Plevova et al., like Tada et al., provide no teachings on the effect of cranial irradiation, or any neuroinflammation arising therefrom, on neurogenesis. Indeed, Plevova et al. is silent on neurogenesis. Accordingly, the combination of references would not allow one to predict with any expectation of success that contacting an individual with a dose of an NSAID will reduce loss of neurogenesis resulting from neuroinflammation.

Moreover, as discussed above, Applicants contend that even if the asserted associations between ischemia or cranial radiation and loss of neurogenesis were inherently true, one of ordinary skill in the art would still not have found obvious the pending claimed invention. As discussed above, the presently claimed invention requires recognition of the effect of neuroinflammation in decreasing neurogenesis. Such a teaching is absent from the cited references. Thus, the methods of the invention are not obvious to one of ordinary skill in the art.

Monje et al. was cited for providing evidence that cranial irradiation results in neuroinflammation, activation of microglial cells and loss of neurogenesis. (p. 6, l. 12-14)

As discussed above, Applicants provide herewith a 1.132 Declaration by Dr. Palmer that states that Monje et al. is the Applicants' own work, and was published within one year of the Applicants' filing date. In view of this Declaration, Monje et al. is not citable with respect to the present invention. Additionally, Applicants submit that to their knowledge, no other references (other than those of the Applicants) exist prior to filing of the pending application that teach that neuroinflammation in general, and cranial irradiation-induced neuroinflammation in particular, results in loss of neurogenesis. Absent any other art provided by the Examiner that may provide such a teaching, Plevova et al. does not remedy the deficiencies of Kondo et al. to provide for the method recited in the pending claims.

In view of the above arguments, reconsideration and withdrawal of the rejection is requested.

III. Claims 1, 3-5, 14 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Brain Res 791: 352-356, 1998), in view of Plevova, (Radiol Oncol 36: 33-40, 2002), as evidenced by Monje et al. (Nat Med 8: 95-962, 2002).

The Examiner asserts that the teachings of Kondo et al. and Plevova et al. are set forth in the above rejections. Kondo et al. or Plevova et al. do not teach contacting the individual with NSAID before or after irradiation. However, since the claims do not specify the criticality in the timing of contacting the individual with NSAID, optimization within prior art conditions or through routine experimentation is obvious to one skilled in the art. (p. 9, l. 13-19)

Applicants submit that, as discussed above, neither the primary reference (Kondo et al), nor the secondary reference (Plevova et al.) teach that neuroinflammation, or more particular, neuroinflammation arising from ionizing radiation, results in loss of neurogenesis. Furthermore, Monje et al., which was cited by the Examiner for providing evidence that cranial irradiation

results in neuroinflammation, activation of microglial cells and loss of neurogenesis, is the Applicants' own work (see the 1.132 Declaration by Dr. Palmer, provided herewith and discussed further above), and therefore may not be used to remedy these deficiencies. Accordingly, the combination of references would not allow one to predict with any expectation of success that contacting an individual with a dose of an NSAID will reduce loss of neurogenesis resulting from neuroinflammation.

Reconsideration and withdrawal of the rejection is requested.

**CONCLUSION**

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-303.

Respectfully submitted,
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